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*Sub  
A9*  
CLAIMS:

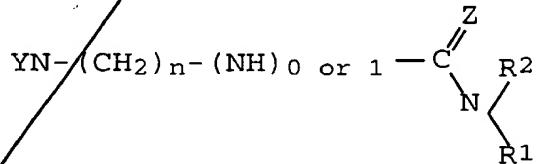
1. An opioid compound of general formula I

5 [opioid-N]-[spacer]-[charged group],

I

in which an opioid compound is linked via the  
nitrogen at position 17 to a spacer group, which in turn is  
10 linked to a charged group,

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, in which the  
spacer is a straight or branched alkyl, alkenyl or alkenyl  
chain of 1 to 6 carbon atoms, which may optionally be  
15 substituted.3. A compound according to Claim 1, in which the  
spacer is a cyclic alkyl, alkenyl or alkynyl group, which  
may optionally be substituted.4. A compound according to any one of Claims 1 to 3,  
in which the spacer group is unsubstituted.5. A compound according to any one of Claims 1 to 4,  
in which the spacer group is of 2 to 3 carbon atoms.6. A compound according to any one of Claims 1 to 5,  
in which the charged group is an amidine or guanidine  
25 group.7. A compound according to Claim 1, of general  
formula (II)

30 in which

YN- represents an organic residue obtained by  
removal of the R group from an opioid compound of general  
formula

YN-R

(IIIa)

5

*Sub*  
*At 10*  
*Cont*

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

10

or of the general formula

Y<sup>1</sup>-N-RR<sup>4</sup>

(IIIb)

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wherein R<sup>4</sup> is methyl or ethyl, and Y<sup>1</sup>-NR<sup>4</sup> represents the corresponding organic residue;

20

Z is O, S or NR<sup>3</sup>;

R<sup>1</sup> is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

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R<sup>2</sup> is H or an alkyl group having 1 to 6 carbon atoms;

R<sup>3</sup> is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

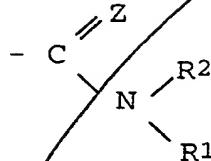
n is an integer of 1 to 6,  
and wherein

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R<sup>1</sup> and R<sup>3</sup> may together complete an addition ring,  
or a pharmaceutically acceptable salt thereof.

8. A compound according to Claim 7, in which R<sup>1</sup> and R<sup>3</sup> together complete an addition ring, and the grouping

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forms a heterocyclic moiety.

9. A compound according to Claim 8, in which the  
5 heterocyclic moiety is a 2-imidazolyl or 2-imidazolinyl  
group of formula:



10. 10. A compound according to Claim 8 or Claim 9, in  
which R is CH<sub>3</sub>.
11. 11. A compound according to any one of Claims 8 to  
10, in which n is 2 or 3.
12. 12. A compound according to any one of Claims 8 to  
15 11, in which Z is NH, and R<sup>1</sup> and R<sup>2</sup> are both H.
13. 13. A compound according to any one of Claims 8 to  
11, in which the precursor of YN- or Y<sup>1</sup>NR<sup>4</sup>- is a compound  
selected from the group consisting of morphine, codeine,  
heroin, ethylmorphine, O-carboxymethylmorphine,  
20 O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone,  
oxycodone, dihydrocodeine, thebaine, metopon, etorphine,  
acetorphine, ketobemidone, ethoheptazine, diprenorphine  
(M5050), buprenorphine, phenomorphan, levorphanol,  
pentazocine, eptazocine and metazocine.
- 25 14. 14. A compound according to Claim 13, in which the  
precursor of YN- or Y<sup>1</sup>NR<sup>4</sup>- is morphine, codeine or  
buprenorphine.
15. 15. A compound according to Claim 1, in which the  
opioid compound of formula (IIIa) or (IIIc) is selected  
30 from the group set out in Table 1.

16. A compound according to Claim 1, in which the compound of general formula I is selected from the group consisting of KRS-41, KRS-2-19, KRS-3-7, KRS-3-23-4, KRS-3-28, KRS-3-30-2, KRS-3-56, KRS-2-63, KRS-4-8, and 5 KRS-2-47, as herein defined.

17. An opiate receptor agonist having analgesic properties and having reduced or no CNS activity, of general formula I or general formula II as defined in any one of claims 1 to 16.

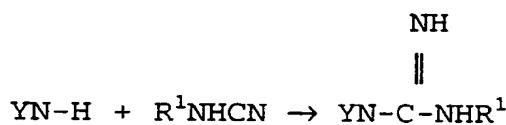
10 18. A method of reducing the central nervous system activity of an opioid compound, comprising the step of linking the nitrogen atom at position 17 of said compound to a spacer group, which in turn is linked to a charged group, optionally via a spacer group.

15 19. A method for the preparation of a compound of formula II as defined in any one of Claims 8 to 14, in which  $Y\text{N}^-$  may be replaced by  $Y^1\text{NR}^4^-$ , comprising the steps of

(a) Reaction of a compound of formula

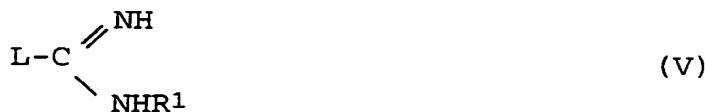
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25 with a cyanamide,  $R^1NHCN$ , according to the  
equation



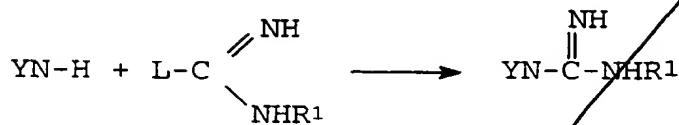
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(b) Reaction of a compound of formula (IV) with a compound of formula



wherein L is a leaving group, according to the equation

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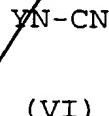


20. A method for the preparation of a compound of formula II as defined in any one of Claims 8 to 14 in which Z is NR<sup>2</sup>, comprising the steps of

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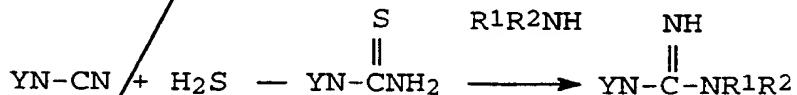
(a) Reaction of a compound of the formula

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with H<sub>2</sub>S to obtain an N-thiocarboxamide YN-CSNH<sub>2</sub>, which is reacted with an amine R<sup>1</sup>R<sup>2</sup>NH according to the two-stage equation

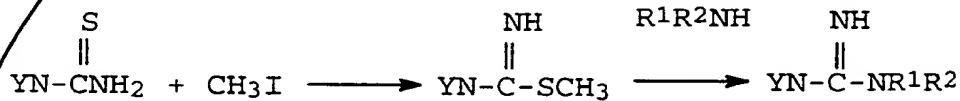
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to yield compounds of the invention where Z is S and where Z is NH, or

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(b) Methylating the N-thiocarboxamide to yield an isothiourea compound, which is in turn reacted with an amine R<sup>1</sup>R<sup>2</sup>NH:



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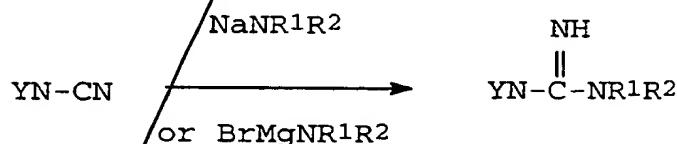
21. A method of synthesis of a compounds of formula (II) as defined in any one of Claims 8 to 14, comprising the step of reacting an N-cyano compound of

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formula (VI) as defined in Claim 19 with methanol under acidic conditions to yield an isourea, which in turn is reacted with an amine according to the equation

$$\begin{array}{ccccc}
 & \text{H}^+ & \text{NH} & \text{R}^1\text{R}^2\text{NH} & \text{NH} \\
 & & \parallel & & \parallel \\
 \text{5} & \text{YN-CN} + \text{CH}_3\text{OH} & \longrightarrow & \text{YN-C(OCH}_3\text{)} & \longrightarrow \text{YN-C-NR}^1\text{R}^2
 \end{array}$$

22. A method of synthesis of a compound of  
formula (II) as defined in any one of Claims 8 to 13 in  
which Z is N, comprising the step of reacting an N-cyano  
10 compound of formula (VI) as defined in Claim 19, and a  
metallated residue



15 23. A composition comprising a compound according to  
any one of Claims 1 to 16, together with a pharmaceutically  
acceptable carrier.

24. A method of inducing analgesia, comprising the  
step of administering an effective amount of a compound  
according to any one of Claims 1 to 16 to a mammal in need  
of such treatment.

25. A method according to Claim 23 in which the mammal is a human.

26. Use of a compound according to any one of  
25 Claims 1 to 16 in medicine. ✓

27. Use of a compound according to any one of Claims 1 to 16 for the manufacture of a medicament for inducing analgesia.

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